DETAILED ACTION

Withdrawal of Finality

The Finality of the Office Action mailed 20 July 2009 is withdrawn.

This Office Action is responsive to Applicant's Amendment and Remarks, filed 20 Oct 2009, entered as a matter of right, in which new claims 14-18 are added.

This application is the national stage entry of PCT/EP03/03327, filed 31 Mar 2003; and claims benefit under 35 USC 119(a-d) of foreign priority document GERMANY 10215942.4, filed 11 Apr 2002; currently an English language translation of this foreign priority document is of record and the claim of foreign priority has been perfected.

Claims 1-18 are pending in the current application and are examined on the merits herein.

Rejections Withdrawn

Applicant's Remarks, filed 20 Oct 2009, with respect to claims 1-4, 8 and 9 rejected under 35 U.S.C. 103(a) as being unpatentable over Mittendorf et al. (US Patent 6,262,112, issued 17 Jul 2001, of record) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001, of record) has been fully considered and is persuasive, as Applicant's

remarks that the use of cyclodextrin in Szabo et al. does not in itself provide sufficient motivation to combine the compound of Mittendorf et al. with cyclodextrin is persuasive.

This rejection has been **withdrawn**.

Applicant's Remarks, filed 20 Oct 2009, with respect to claims 1- 9 rejected under 35 U.S.C. 103(a) as being unpatentable over Mittendorf et al. (US Patent 6,262,112, issued 17 Jul 2001, of record) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001) and Nakazi et al (Naunyn-Schmiedeberg's Arch. Pharmacol., 2000) has been fully considered and is persuasive, as Applicant's remarks that the use of cyclodextrin in Szabo et al. does not in itself provide sufficient motivation to combine the compound of Mittendorf et al. with cyclodextrin is persuasive.

This rejection has been **withdrawn**.

Applicant's Remarks, filed 20 Oct 2009, with respect to claims 1-4 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mittendorf et al. (US Patent 6,262,112, issued 17 Jul 2001, of record) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001) and Yamada (US 5,807,337) has been fully considered and is persuasive, as Applicant's remarks that the use of cyclodextrin in Szabo et al. does not in itself provide sufficient motivation to combine the compound of Mittendorf et al. with cyclodextrin is persuasive.

This rejection has been **withdrawn**.

The following are new grounds of rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 1-4, 8, 9 and 11-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mittendorf et al. (US Patent 6,262,112, issued 17 Jul 2001, of record) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001, of record) and Liu (Water-Insoluble Drug Formulation, 2000, p111-140, of record) and Loftsson et al. (Journal of Pharmaceutical Sciences, 1996, 85(10), p1017-1025, provided by Applicant in IDS mailed 08 Oct 2004).

Mittendorf discloses a pharmaceutical composition comprising the compound (-)-(R)-3-(2-hydroxymethylindanyl-4-oxy)phenyl 4,4,4-trifluorobutane-1-sulfonate (column

199, claim 1 and column 200, claim 5). Mittendorf discloses the compound is a cannabinoid receptor agonist (column 1, lines 23-50). This composition is suitable for administration as a continuous infusion (column 36, lines 55-58). Mittendorf discloses the composition wherein the solvent is aqueous NaCl (column 36, lines 15-20). Mittendorf discloses the compound with suitable excipients and envisions the use of organic solvents as auxiliary solvents if water is used as a diluent (column 37, lines 20-30). Mittendorf discloses the dosage of the compound of 0.01 to 10 mg/kg (column 37, lines 35-37).

Mittendorf does not specifically disclose the excipient cyclodextrin or the ratio of compound to cyclodextrin.

Szabo teaches that an aqueous solution diluted with a 19% cyclodextrin solution is a suitable vehicle for infusing the cannabinoid receptor agonists, WIN 55,212-2 and CP 55,940. See page 820, 2nd paragraph under "Drugs." The reference further teaches that other similar drugs are dissolved in ethanol and saline.

Liu teaches the technique of solubility enhancement by applications of cyclodextrin is well known (page 111, paragraph 1). Liu teaches the structural aspects of complexation largely depends on the complexed compound's size compatibility with the dimensions of the CD cavities (page 115, especially paragraph 1). Liu teaches it is routine optimization of concentration of CD to form 1:1 or 2:1 CD:guest complex. (page 116, paragraph 2). Liu teaches many examples are known to demonstrate the effect of CD on solubility, dissolution rates, and bioavailability of poorly water soluble compounds (page 126, paragraph 5 at bottom of page) as well as by mechanisms not requiring

complexation by altering the lipid barrier at the absorption site (page 127, paragraph 2). Liu teaches known advantages of CD inclusion for solid preparations for content uniformity, liquid preparations are improved solubility and stability, and for injectable preparations reduction of drug-induced hemolysis and muscular tissue damage, and ease of formulating solid preparations into liquid preparations (page 127, at bottom of page and page 128, 5. Injectable Preparations at middle of page).

Loftsson et al. teaches it is well known that the pharmaceutical applications of cyclodextrin are for drug solubilization and stabilization. Loftsson et al. teaches the methods of preparing drug-cyclodextrin complexes are known to be routine in the art and well within the level ordinary skill in the art (page 1020, left column, paragraph 2). Loftsson et al. teaches it is routine in the art to optimize the concentration of cyclodextrin, teaching examples of 1.5, 10, 15 and 50 %w/v, (page1021, table 5 at top of page). Loftsson et al. teaches molecules may also form complexes with drug molecules like peptides and proteins that is qualitatively different from the complexes with small molecular weight compounds, with the maximum benefit obtained at low cyclodextrin concentrations and the benefits are only partly concentration dependent (page 1024, left column, paragraph 2).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Mittendorf et al. in view of Szabo et al and Liu and Loftsson et al. One of ordinary skill in the art would be motivated to combine Mittendorf in view of Szabo et al and Liu and Loftsson et al. because Mittendorf et al. suggests the compound of Mittendorf et al. is water-insoluble requiring organic solvents as auxiliary

solvents if water is used as a diluent and Liu and Loftsson et al. teach it is well known that cyclodextrin is used to improve solubility of water-insoluble compounds. Further, one of ordinary skill in the art would be motivated to select cyclodextrin as the agent used to improve solubility of water-insoluble compounds because Szabo et al, drawn to infusing the cannabinoid receptor agonists as compositions comprising cyclodextrin, suggests the use of a known technique to improve similar products in the same way. Liu and Loftsson teach it would have been routine experimentation for one of ordinary skill in the art to optimize the concentration of cyclodextrin within the range of 1.5 to 50 % w/v based on the amount of guest compound.

Response to Applicant's Remarks:

Applicant's Remarks, filed 20 Oct 2009, have been fully considered and not found to be persuasive in view of the new grounds of rejection.

Applicant's remarks that the use of cyclodextrin in Szabo et al. does not in itself provide sufficient motivation to combine the compound of Mittendorf et al. with cyclodextrin is persuasive. However, new grounds of rejection are made in view of the teaching of Mittendorf that the compound of Mittendorf et al. is water-insoluble in view of the teaching of Liu and the teaching of Loftsson et al. that it is well known that cyclodextrin is used to improve solubility of water-insoluble compounds.

Applicant notes that Liu discloses examples wherein the complex does not form. However, Liu discloses the correlation between binding strength and guest molecule sturctural features is limited within certain groups of compounds and no obvious correlation has been found between different families of guest molecules (page 116,

paragraph 4 at bottom of page). Further, MPEP 2143.02 provides at I. "The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success" and at II. "Obviousness does not require absolute predictability, however, at least some degree of predictability is required." Liu disclosing the strong guest size dependence for complex formation would provide some degree of predictability such that one of ordinary skill in the art would have a reasonable expectation of success in combining the prior art.

Applicant notes Liu discloses examples wherein the structural features of other families of guest compounds result in compounds that do not form complexes with cyclodextrin. However, in view of the disclosure of Liu that no obvious correlation has been found between different families of guest molecules, this evidence is not persuasive for the instant family of guest compounds. While evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness, in view of the teaching of Liu that this evidence does not apply to other families of guest compounds, the degree of predictability taught by Liu is still found sufficient to support a *prima facie* case obvious.

Applicant notes that Szabo does not teach improving any inhomogenous concentration distribution of any compound, and therefore this result is unexpected based on the teaching of Mittendorf et al. in view of Szabo. New grounds of rejection are made in view of the teaching of Mittendorf that the compound of Mittendorf et al. is water-insoluble in view of the teaching of Liu and the teaching of Loftsson et al. that it is well known that cyclodextrin is used to improve solubility of water-insoluble compounds,

and one of ordinary skill in the art would expect that improved solubility would result in improved homogenous concentration distribution in solution because of said improved solubility.

It is further noted that the instant invention as claimed requires no relationship between the concentration of compound (I) and cyclodextrin. For example, instant claim 2 encompasses ratios of 0.00005 g/l of compound (I) and 550 g/l cyclodextrin (1:11,000,000 by weight) to 9.0 g/l of compound (I) and 0.1 g/l cyclodextrin (90:1 by weight). Instant claim 4 encompasses ratios of 0.0005 g/l of compound (I) and 50 g/l cyclodextrin (1:100,000 by weight) to 0.025 g/l of compound (I) and 1 g/l cyclodextrin (1:40 by weight). As disclosed by Loftsson et al. molecules may also form complexes with drug molecules like peptides and proteins that is qualitatively different from the complexes with small molecular weight compounds, with the maximum benefit obtained at low cyclodextrin concentrations and the benefits are only partly concentration dependent and Liu teaches CD causes improvements by mechanisms not requiring complexation by altering the lipid barrier at the absorption site. Therefore the instant invention as claimed does not appear to require an inclusion complex having a fixed stoichiometric ratio. Loftsson et al. and Liu provide a reasonable expectation of success in improving the compound taught by Mittendorf et al. in complexes qualitatively different from the inclusion complexes with small molecular weight compounds because said improvements are due solely to the presence of cyclodextrin in the composition.

Amended Claims 1-9 and 11-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mittendorf et al. (US Patent 6,262,112, issued 17 Jul 2001, of record) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001, of record) and Liu (Water-Insoluble Drug Formulation, 2000, p111-140, of record) and Loftsson et al. (Journal of Pharmaceutical Sciences, 1996, 85(10), p1017-1025, provided by Applicant in IDS mailed 08 Oct 2004) and Nakazi et al (Naunyn-Schmiedeberg's Arch. Pharmacol., 2000).

Mittendorf et al. in view of Szabo et al and Liu and Loftsson et al. teach as set forth above.

The references are silent regarding the pH of the solutions or the use of citric acid.

Nakazi teaches that a citrate buffer (pH 4.8) is a suitable vehicle for cerebral infusion of the cannabinoid agonists, WIN 55,212-2 and CP 55,940. See paragraph bridging pages 20 and 21.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare a composition comprising said compound for infusion using any suitable physiologically solution for administration as taught by Mittendorf. One of ordinary skill would use a vehicle known to be used for other similar therapeutic compounds, such as the aqueous solution comprising a cyclodextrin, with a reasonable expectation of success. In the absence of unexpected results, it would be further obvious to modify this composition by adjusting it to a suitable pH for cerebral infusion with a citrate buffer with a reasonable expectation of success.

The instant claims recite a composition comprising compound (I) and various standard physiological excipients. However, the examiner does not find there to be any evidence of criticality in any particular mix of components.

Response to Applicant's Remarks:

Applicant's Remarks, filed 20 Oct 2009, have been fully considered and not found to be persuasive in view of the new grounds of rejection.

Applicant's remarks regarding Mittendorf et al. in view of Szabo et al. are address as above and in view of new grounds of rejection over Mittendorf et al. in view of Szabo et al. and Liu and Loftsson et al.

Amended Claims 1-4 and 8-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mittendorf et al. (US Patent 6,262,112, issued 17 Jul 2001, of record) in view of Szabo et al (J. Pharmacol. Exp. Ther., 2001, of record) and Liu (Water-Insoluble Drug Formulation, 2000, p111-140, of record) and Loftsson et al. (Journal of Pharmaceutical Sciences, 1996, 85(10), p1017-1025, provided by Applicant in IDS mailed 08 Oct 2004) and Yamada (US 5,807,337, of record).

Mittendorf et al. in view of Szabo et al. and Liu and Loftsson et al. teach as set forth above.

The references teach the infusion of cannabinoid receptor agonists but are silent regarding the description of the infusion apparatus used in each reference.

It is well known in the art to use an infusion apparatus for the continuous administration of therapeutic agents, and the drug-contacting surfaces are typically plastic. See, for example, Yamada at col 5, lines 15-25.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare the recited composition, as set forth above. It would be further obvious to combine the composition with an infusion apparatus to form a kit for administration of the composition. It would be within the scope of the artisan to select any appropriate apparatus for this utility.

Response to Applicant's Remarks:

Applicant's Remarks, filed 20 Oct 2009, have been fully considered and not found to be persuasive in view of the new grounds of rejection.

Applicant's remarks regarding Mittendorf et al. in view of Szabo et al. are address as above and in view of new grounds of rejection over Mittendorf et al. in view of Szabo et al. and Liu and Loftsson et al.

Conclusion

No claim is found to be allowable.

This Office Action details new grounds of rejection not necessitated by Applicant's Amendment. Accordingly, this Office Action is Non-Final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-

3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jonathan Lau
Patent Examiner
Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner
Art Unit 1623